Amendments to the claims

Claim 1 is amended to overcome the 35 U.S.C. §102(b) rejection by incorporating the elements of canceled claim 5, and for reasons of clarity. Claim 11 is amended to overcome the 35 U.S.C. 112, second paragraph rejection of claims 11-13, according to suggestions helpfully made by the Examiner. No new matter has been added.

The 35 U.S.C. §112, second paragraph rejection

Claims 11-13 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is respectfully traversed. As helpfully suggested by the Examiner, independent claim 11 is amended to recite "administering said drug," for which there is a proper antecedent basis; therefore, the meaning of claim 11 and dependent claims 12-13 is clarified. Accordingly, Applicants respectfully request that the rejection of claims 11-13 under 35 U.S.C. §112, second paragraph, be withdrawn.

The 35 U.S.C. §102(b) rejections

Claims 1-2 and 5 are rejected under 35 U.S.C. §102(b) as being anticipated by **Yan** *et al.* (*Circulation* 96(8): Suppl. P. 1605 (1997)). This rejection is respectfully traversed.

Yan teaches assaying normal and diseased human aortic tissues for mitochondrial DNA damage using quantitative PCR, where the aortic tissues in samples with evidence of atherosclerosis contained a higher degree of mitochondrial DNA damage than in the normal tissues. Measured levels of hydrogen peroxide, superoxide anion, and lipid peroxidation products were consistent with the association of reactive oxygen species-induced mitochondrial DNA damage with atherosclerosis. However, **Yan** does not teach the measurement of mitochondrial DNA damage by measuring mitochondrial mRNA or protein production, or changes in mitochondrial oxidative phosphorylation or ATP production. Therefore, **Yan** does not teach each and every element of amended claim 1, and therefore does not anticipate claim 1 or dependent claim 2. The rejection of claim 5 is moot, as claim 5 has been cancelled. Accordingly, Applicants respectfully request that the rejection of claims 1-2 and 5 under 35 U.S.C. §102(b) be withdrawn.

Claims 1-2 and 5 are rejected under 35 U.S.C. §102(b) as being anticipated by **Corral-Debrinski** *et al.* (*Mut. Res.* 275: 169-180 (1992)). This rejection is respectfully traversed.

Corral-Debrinski teaches quantitative PCR to compare the levels of a common 4977 base-pair deletion in mitochondrial DNA, and the transcript levels of nuclear and mitochondrial DNA oxidative phosphorylation genes. between post-mortem heart samples from normal individuals and individuals with coronary atherosclerotic disease. However, **Corral-Debrinski** fails to anticipate the instant invention in that **Corral-Debrinski** does not teach a method of evaluating the atherosclerotic state of an individual.

Unlike Applicants' claimed invention, **Corral-Debrinski** analyzed cardiac tissues from pathology samples. **Corral-Debrinski** provides no teaching that one could analyze mitochondrial damage in the actual tissues involved in atherosclerosis, specifically the arteries and the blood. To use the method of **Corral-Debrinski** to assess mitochondrial damage, one would have to obtain a sample of cardiac tissues from the patient in question. In contrast, Applicants' claimed invention demonstrates that DNA damage due to atherosclerosis occurs in arterial tissue and can be assayed from blood samples.

Corral-Debrinski provides no evidence that DNA damage due to atherosclerosis can be assayed from a blood or aortic tissue sample.

Corral-Debrinski examined damaged hearts from deceased patients. Therefore, a portion of the observed abnormalities could be the result of events that occurred during death or the events leading up to death. Furthermore, it has been well known in the art that the mitochondria of damaged hearts are abnormal. Therefore, from **Corral-Debrinski,** it can not be determined whether the observed mutation levels in the heart tissue samples were specific to atherosclerosis or whether they were due to other causes. Moreover, because **Corral-Debrinski** examined heart tissue from deceased individuals, no association can be made between the observed damage and the progression of atherosclerosis. Consequently, **Corral-Debrinski** provides no evidence or teaching for a method useful as a predictive test for the development of atherosclerosis.

The PCR amplification of **Corral-Debrinski** was limited to the detection of mutations in the mitochondrial DNA of the heart tissue. In contrast, Applicants' describes the measurement of oxidative damage in the mitochondrial DNA template as well as mutations by treating the DNA with FAPY glycosylase prior to PCR

amplification to enable detection of 8-oxo-deoxyguanosine lesions. This procedure makes the assay more sensitive in that it is possible to detect reversible oxidative lesions as well as mutations. Thus, the instant invention can also be used to analyze the effects of changes that reduce oxidative risk such as cessation of smoking or dietary changes. This cannot be done with the method of **Corral-Debrinski** *et al.*

As **Corral-Debrinski** reference fails to anticipate the instant invention for several reasons, Applicants respectfully request that the rejection of claims 1-2 and 5 under 35 U.S.C. §102(b) as lacking novelty over **Corral-Debrinski** be withdrawn.

The 35 U.S.C. §103(a) rejection

Claims 11-13 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Yan** *et al.* (*Circulation* 96(8): Suppl. P. 1605 (1997)) or **Corral-Debrinski** *et al.* (*Mut. Res.* 275: 169-180 (1992)) in further view of **Herrnstadt** *et al.* (U.S. Pat. No. 6,218,117). Applicants respectfully traverse this rejection.

Herrnstadt teaches the quantification of the ratio of extramitochondrial to mitochondrial DNA in a sample to detect a predisposition to diseases associated with altered mitochondrial

function, and a possible treatment for such a disease by identifying a candidate agent that is able to affect the quantified ratio when contacted with the sample. However, **Herrnstadt** teaches only the quantification of the relative amounts of extramitochondrial and mitochondrial DNA in a sample, and does not teach or suggest the measurement of the amount of mitochondrial DNA damage in a sample to assess the risk of atherosclerosis in an individual. The instant invention does not compare the relative amounts of mitochondrial and extramitochondrial DNA to assess the efficacy of a drug. Instead, the level of mitochondrial DNA damage is compared before and after administration of the drug to an individual. **Corral-Debrinski** does not suggest the analysis of DNA from tissues other than cardiac tissue and does not suggest the analysis of DNA from a sample obtained from a living patient. Furthermore, there is no discussion of a method to detect oxidative lesions in DNA in **Corral-Debrinski** but only DNA deletions. Neither **Yan** nor **Corral-Debrinski** teaches or suggests a method of determining the efficacy of a drug by administering the drug to a sample and determining the level of mitochondrial DNA damage.

Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention absent

some teaching, suggestion, or incentive supporting the combination. *In re Bond*, 910 F.2d 831, 834 (Fed. Cir. 1990). Applicants respectfully submit that no such teaching, suggestion or incentive may be gleaned from the references relied upon by the Examiner. There is no suggestion to combine the testing of a candidate agent from **Herrnstadt** with the assessment of mitochondrial DNA damage in either **Yan** or **Corral-Debrinski** to arrive at the claimed method of determining the efficacy of a drug to reduce the risk of atherosclerosis in an individual, by determining the amount of mitochondrial DNA damage in a tissue of interest collected from said individual before and after administering said drug to said individual. Such a combination requires the teachings of the present invention; therefore, the rejection of claims 11-13 over the cited references constitutes an impermissible hind-sight rejection. *W. L. Gore & Associates v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983). Accordingly, Applicants respectfully request that the rejection of claims 11-13 under 35 U.S.C. §103(a) be withdrawn.

The Double Patenting rejection

Claims 1-13 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable

over claims 1-13 of U.S. Pat. No. 6,322,974. Applicants submit a terminal disclaimer under 37 CRF 1.130(b), in compliance with 37 CFR 1.321(c). Accordingly, Applicants respectfully request that the obviousness-type double patenting rejection of claims 1-13 be withdrawn.

This is intended to be a complete response to the Office Action mailed November 20, 2002. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: Dec 16, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Please amend claim 1 as follows:

1. (Amended) A method of evaluating the atherosclerotic state of an individual, comprising the steps of:

(d) collecting a tissue of interest from said individual;

(e) determining the amount of mitochondrial DNA damage in said tissue of interest; and

(f) comparing the amount of mitochondrial DNA damage in the tissue of interest from said individual to the amount of mitochondrial DNA damage in a tissue of interest from a control individual who does not have atherosclerosis, wherein a greater amount of mitochondrial DNA damage in said individual at risk than in said control individual is indicative of atherosclerosis in said individual, wherein said mitochondrial DNA damage is assessed by a measurement selected from the group consisting of measurement of mitochondrial mRNA production, measurement of mitochondrial protein production, measurement of changes in mitochondrial oxidative phosphorylation and measurement of changes in mitochondrial ATP production.

Please cancel claim 5.

Please amend claim 11 as follows:

11. (Amended) A method of determining the efficacy of a drug to reduce the risk of atherosclerosis in an individual, comprising the steps of:

(c) collecting a tissue of interest from said individual prior to and subsequent to administering said drug to said individual; and

(d) determining the amount of mitochondrial DNA damage in said tissue of interest collected, wherein a decrease in mitochondrial DNA damage subsequent to ~~said treatment~~ administering said drug is indicative of a treatment that reduces the risk of atherosclerosis.